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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
BOWMAN, AMY HUDSON

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,129	LI ET AL.	
	Examiner	Art Unit	
	AMY H. BOWMAN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-63* is/are pending in the application.

4a) Of the above claim(s) *1-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 March 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/7/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse of group III, claims 36-63 and SEQ ID NO: 1, in the reply filed on 1/4/08 is acknowledged.

Claims 1-35 and the subject matter of claim 43 that is not directed to SEQ ID NO: 1 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 1/4/08. It is noted that the broad claims are not directed to a specific siRNA sequence and the full scope will be examined. However, claim 44 recites a specific siRNA sequence and will be examined as the elected siRNA.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 6/7/06 has been considered by the examiner.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 57 and 60-62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 57 recites the limitation "at least one siRNA molecule of claim 36". There is insufficient antecedent basis for this limitation in claim 36 because claim 36 is directed to a single siRNA molecule, rather than at least one siRNA. Claims 60-62 are rejected because they depend from claim 57.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36-42 and 45-63 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

At the outset, it is noted that the claims do not recite a specific HIF-1α nucleotide sequence by SEQ ID NO, but rather refer to the broad genus of HIF-1α sequences.

The claims encompass siRNA molecules that down regulate the expression of any HIF-1α sequence, as well as encompass siRNA directed to any HIF-1α homolog or allele from any species known or yet to be discovered of HIF-1α, as well as DNA genomic fragments, spliced variants or fragment that retains HIF-1α-like activity.

Although the specification discloses siRNA molecules directed to SEQ ID NO: 1 or 3 (one human or one mouse sequence, respectively), the specification does not describe siRNA molecules directed to any other HIF-1α sequence to demonstrate that

applicant was in possession of the instant genus of siRNA molecules directed to any HIF-1α sequence. One of ordinary skill in the art could not make such siRNA molecules to any HIF-1α without knowledge of the sequence. Given the breadth of sequences embraced in the instantly claimed genus, one could not envision the member agents that target such a broad genus.

For example, Reich et al. (WO 2004/042024) teach that human HIF-1α includes mutant or alternative splice forms of human HIF-1α mRNA, or mRNA from cognate HIF-1α genes. Reich et al. teaches that splice variants of human HIF-1α are known, including HIF-1α transcript variants 1 and 2 as described in GenBank accession numbers NM_001530 and NM_181054 (see page 5 of Reich et al.). Furthermore, Reich et al. discloses human, rat and mouse HIF-1α sequences (see page 7, for example). The instant specification discloses that in some embodiments, the HIF-1α gene comprises a nucleotide sequence of one of SEQ ID NOs: 1 and 3 (see page 6) and thus does not describe an adequate species of HIF-1α target sequences to describe the entire genus of HIF-1α sequences.

Therefore, the skilled artisan would not be able to envisage the entire genus of claimed siRNA molecules directed to any HIF-1α such that the skilled artisan would recognize that the applicant was in possession of the claimed genus at the time of filing.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 36 is rejected under 35 U.S.C. 102(e) as being anticipated by Yoon et al. (US 7,205,283 B2), as evidenced by Holen et al. (Nucleic Acids Research, 2003, Vol. 31, No. 9, pp. 2401-2407).

The instant claim is directed to a small interfering RNA (siRNA) molecule that down regulates expression of a hypoxia-inducible factor 1α (HIF-1α) gene by RNA interference.

It is noted that the instant specification does not define the term "siRNA" to exclude single stranded oligonucleotides. Yoon et al. teach antisense oligonucleotides that meet the instant limitation of being a small interfering RNA, wherein the antisense oligonucleotides down regulate the expression of HIF-1α (see Table 1, for example). Yoon et al. teach that the oligonucleotides can be oligomers or polymers of RNA or DNA (see column 3). Although Yoon et al. does not specifically teach that the small interfering RNAs act via RNA interference, it was known in the art at the time the invention was made that single stranded oligonucleotides can act through the RNAi pathway, as evidenced by Holen et al.

Therefore, the instant invention is anticipated by Yoon et al., as evidenced by Holen et al.

Claims 36-41, 43, 45-49, 52, 53, and 56-63 are rejected under 35 U.S.C. 102(e) as being anticipated by Reich et al. (WO 2004/042024 A2).

The instant claims are directed to a small interfering RNA (siRNA) molecule that down regulates expression of a hypoxia-inducible factor 1α (HIF-1α) gene by RNA interference. The claims are further directed to structural requirements of the siRNA, linkers, modifications, terminal caps, vectors, and cells comprising the vectors.

Reich et al. teaches siRNA molecules that target HIF-1α mRNA and inhibit the expression of the HIF-1α gene via RNA interference (see abstract and page 3, for example). Reich et al. teach siRNA and pharmaceutical compositions thereof which target HIF-1α (see page 3). Reich et al. teach that the siRNA molecules have a first strand that is the same nucleotide sequence as a portion of the HIF-1α mRNA sequence and have a second strand of the siRNA duplex that is complementary to both the first strand of the RNA duplex and the same portion of the HIF-1α mRNA. (see page 4). The siRNA duplexes are about 17 nucleotides to 29 nucleotides in length, more preferably about 19 to about 25 nucleotides in length (see page 4). Reich et al. teach suitable human HIF-1α target sequences on pages 9, 10 and 25.

Reich et al. teach that the siRNA can comprise two separate strands or can comprise a single molecule in which two complementary portions are base-paired and are covalently linked by a single-stranded hairpin area (see page 5), meeting the instant limitation of a nucleotide linker.

Reich et al. teach that the siRNA can contain modifications of one or more ribonucleotide bases and can contain one or more deoxyribonucleotide bases (see

page 5). Reich et al. teach that the siRNA can be altered by the addition of non-nucleotide material, such as to the ends of the siRNA or to one or more internal nucleotides of the siRNA, meeting the instant limitation of a terminal cap. Reich et al. teach that the siRNA can be modified with modifications that make the siRNA resistant to nuclease digestion (see page 7).

Reich et al. teach that the siRNA can also comprise a 3'-overhang on one or both strands and that is 1 to 6 , more preferably 1 to 5, more preferably 1 to about 4, more preferably about 2 to about 4 nucleotides in length (see pages 7 and 8). The overhangs can be modified with dithymidylic acid (TT) or diuridylic acid (UU). Reich et al. teach that in order to enhance stability of the siRNA, the 3' overhangs can be stabilized against degradation by substitution by modified analogues (see page 8).

Reich et al. teach that the siRNA can be expressed from plasmids using any suitable promoter either as two separate, complementary RNA molecules or as a single RNA molecule with two complementary regions (see page 11). Reich et al. teach that the siRNA can be expressed from recombinant viral vectors and delivered to human cells (see page 12, for example). The siRNA molecules can be expressed from a recombinant viral vector either as two separate complementary nucleic acid molecules or as a single nucleic acid molecule with two complementary regions. The viral vector can be derived from adenovirus (see page 13).

Reich et al. teach compositions comprising the siRNA molecules and pharmaceutically acceptable carriers (see claim 28).

Therefore, the instant invention is anticipated by Reich et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 36-43 and 45-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reich et al. (WO 2004/042024 A2), as explained in the rejection under 35 U.S.C. 102(e), above, in view of Fosnaugh et al. (US 2003/0143732 A1).

The instant claims are directed to a small interfering RNA (siRNA) molecule that down regulates expression of a hypoxia-inducible factor 1α (HIF-1α) gene by RNA interference. The claims are further directed to structural requirements of the siRNA, linkers, modifications, terminal caps, vectors, and cells comprising the vectors.

Reich et al. teaches siRNA molecules that target HIF-1α mRNA and inhibit the expression of the HIF-1α gene via RNA interference (see abstract and page 3, for example). Reich et al. teach siRNA and pharmaceutical compositions thereof which

target HIF-1α (see page 3). Reich et al. teach that the siRNA molecules have a first strand that is the same nucleotide sequence as a portion of the HIF-1α mRNA sequence and have a second strand of the siRNA duplex that is complementary to both the first strand of the RNA duplex and the same portion of the HIF-1α mRNA. (see page 4). The siRNA duplexes are about 17 nucleotides to 29 nucleotides in length, more preferably about 19 to about 25 nucleotides in length (see page 4). Reich et al. teach suitable human HIF-1α target sequences on pages 9, 10 and 25.

Reich et al. teach that the siRNA can comprise two separate strands or can comprise a single molecule in which two complementary portions are base-paired and are covalently linked by a single-stranded hairpin area (see page 5), meeting the instant limitation of a nucleotide linker.

Reich et al. teach that the siRNA can contain modifications of one or more ribonucleotide bases and can contain one or more deoxyribonucleotide bases (see page 5). Reich et al. teach that the siRNA can be altered by the addition of non-nucleotide material, such as to the ends of the siRNA or to one or more internal nucleotides of the siRNA, meeting the instant limitation of a terminal cap. Reich et al. teach that the siRNA can be modified with modifications that make the siRNA resistant to nuclease digestion (see page 7).

Reich et al. teach that the siRNA can also comprise a 3'-overhang on one or both strands and that is 1 to 6 , more preferably 1 to 5, more preferably 1 to about 4, more preferably about 2 to about 4 nucleotides in length (see pages 7 and 8). The overhangs can be modified with dithymidylic acid (TT) or diuridylic acid (UU). Reich et al. teach

that in order to enhance stability of the siRNA, the 3' overhangs can be stabilized against degradation by substitution by modified analogues (see page 8).

Reich et al. teach that the siRNA can be expressed from plasmids using any suitable promoter either as two separate, complementary RNA molecules or as a single RNA molecule with two complementary regions (see page 11). Reich et al. teach that the siRNA can be expressed from recombinant viral vectors and delivered to human cells (see page 12, for example). The siRNA molecules can be expressed from a recombinant viral vector either as two separate complementary nucleic acid molecules or as a single nucleic acid molecule with two complementary regions. The viral vector can be derived from adenovirus (see page 13).

Reich et al. teach compositions comprising the siRNA molecules and pharmaceutically acceptable carriers (see claim 28).

Although Reich et al. teaches utilizing nucleotide linker hairpin regions, Reich et al. do not teach non-nucleotide linkers. Although Reich et al. teaches modifying siRNA molecules to enhance resistance to nuclease digestion, Reich et al. do not specifically teach phosphorothioate nucleotides, universal bases ribonucleotides, or acyclic nucleotides.

Fosnaugh et al. teach siRNA molecules assembled from two separate fragments, wherein one fragment comprises the sense region and the other fragment comprises the antisense region. The fragments can be covalently connected via a linker molecule, wherein the linker molecule can be a polynucleotide linker or a non-nucleotide linker. The siRNA molecules can comprise modified purines or pyrimidines. Fosnaugh et al.

teach phosphorothioates at the 3' end of the antisense region, one to five phosphorothioates at the 5' end of the antisense region, and modifications to the 3' terminal overhangs including universal bases or acyclic nucleotides. Fosnaugh et al. teach that chemical modifications of siRNA constructs dramatically increase serum stability, improve the stability of the interaction with target RNA sequences, and improve nuclease resistance.

It would have been obvious to one of ordinary skill in the art to incorporate the specific structural configurations and chemical modifications of the siRNAs of Fosnaugh et al. into the siRNA molecules specific for HIF-1α of Reich et al.

One would have been motivated to incorporate the specific structural configurations and chemical modifications of the siRNAs of Fosnaugh et al. into the siRNA molecules specific for HIF-1α of Reich et al. because Reich et al. teaches the concept of incorporating chemical modifications to increase siRNA resistance to nuclease digestion and incorporating a hairpin configuration. Since Reich et al. teach these elements, one would have certainly been motivated to incorporate other linkers or chemical modifications that were known to add the same benefits to siRNA molecules, as taught by Fosnaugh et al. Fosnaugh et al. teach that chemical modifications of siRNA constructs dramatically increase serum stability, improve the stability of the interaction with target RNA sequences, and improve nuclease resistance.

It would have been prima facie obvious to perform routine optimization to determine the optimal structural configuration (i.e. presence of linkers) and optimal chemical modifications of the siRNA molecules, as noted in *In re Aller*, 105 USPQ 233

at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the particular chemical modifications or linkers used was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

One would have a reasonable expectation of success given that each of the modifications and linkers were known in the art at the time the invention was made to add benefits to siRNA molecules, as evidenced by both Reich et al. and Fosnaugh et al. One would reasonably expect for the modifications and structural elements of the siRNA molecules of Fosnaugh et al. to yield the same benefits to the siRNA molecules targeted to HIF-1α of Reich et al.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 36-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reich et al. (WO 2004/042024 A2), in view of Fosnaugh et al. (US 2003/0143732 A1), as explained in the rejection under 35 U.S.C. 103(a) above, further in view of the

Ambion siRNA target finder

(http://www.ambion.com/techlib/misc/siRNA_finder.html, available 2002 to the public).

The instant claims are directed to a small interfering RNA (siRNA) molecule that down regulates expression of a hypoxia-inducible factor 1α (HIF-1α) gene by RNA interference. The claims are further directed to structural requirements of the siRNA, linkers, modifications, terminal caps, vectors, and cells comprising the vectors. Instant claim 44 requires for the sense region of the siRNA to comprise instant SEQ ID NO: 7. This is the limitation that necessitates the instant rejection compared to the previous rejection under 35 U.S.C. 103(a).

Reich et al. teaches siRNA molecules that target HIF-1α mRNA and inhibit the expression of the HIF-1α gene via RNA interference (see abstract and page 3, for example). Reich et al. teach siRNA and pharmaceutical compositions thereof which target HIF-1α (see page 3). Reich et al. teach that the siRNA molecules have a first strand that is the same nucleotide sequence as a portion of the HIF-1α mRNA sequence and have a second strand of the siRNA duplex that is complementary to both the first strand of the RNA duplex and the same portion of the HIF-1α mRNA. (see page 4). The siRNA duplexes are about 17 nucleotides to 29 nucleotides in length, more preferably about 19 to about 25 nucleotides in length (see page 4). Reich et al. teach suitable human HIF-1α target sequences on pages 9, 10 and 25.

Reich et al. teach that the siRNA can comprise two separate strands or can comprise a single molecule in which two complementary portions are base-paired and

are covalently linked by a single-stranded hairpin area (see page 5), meeting the instant limitation of a nucleotide linker.

Reich et al. teach that the siRNA can contain modifications of one or more ribonucleotide bases and can contain one or more deoxyribonucleotide bases (see page 5). Reich et al. teach that the siRNA can be altered by the addition of non-nucleotide material, such as to the ends of the siRNA or to one or more internal nucleotides of the siRNA, meeting the instant limitation of a terminal cap. Reich et al. teach that the siRNA can be modified with modifications that make the siRNA resistant to nuclease digestion (see page 7).

Reich et al. teach that the siRNA can also comprise a 3'-overhang on one or both strands and that is 1 to 6 , more preferably 1 to 5, more preferably 1 to about 4, more preferably about 2 to about 4 nucleotides in length (see pages 7 and 8). The overhangs can be modified with dithymidylic acid (TT) or diuridylic acid (UU). Reich et al. teach that in order to enhance stability of the siRNA, the 3' overhangs can be stabilized against degradation by substitution by modified analogues (see page 8).

Reich et al. teach that the siRNA can be expressed from plasmids using any suitable promoter either as two separate, complementary RNA molecules or as a single RNA molecule with two complementary regions (see page 11). Reich et al. teach that the siRNA can be expressed from recombinant viral vectors and delivered to human cells (see page 12, for example). The siRNA molecules can be expressed from a recombinant viral vector either as two separate complementary nucleic acid molecules

or as a single nucleic acid molecule with two complementary regions. The viral vector can be derived from adenovirus (see page 13).

Reich et al. teach compositions comprising the siRNA molecules and pharmaceutically acceptable carriers (see claim 28).

Fosnaugh et al. teach siRNA molecules assembled from two separate fragments, wherein one fragment comprises the sense region and the other fragment comprises the antisense region. The fragments can be covalently connected via a linker molecule, wherein the linker molecule can be a polynucleotide linker or a non-nucleotide linker. The siRNA molecules can comprise modified purines or pyrimidines. Fosnaugh et al. teach phosphorothioates at the 3' end of the antisense region, one to five phosphorothioates at the 5' end of the antisense region, and modifications to the 3' terminal overhangs including universal bases or acyclic nucleotides. Fosnaugh et al. teach that chemical modifications of siRNA constructs dramatically increase serum stability, improve the stability of the interaction with target RNA sequences, and improve nuclease resistance.

Reich et al. and Fosnaugh et al. do not teach siRNA molecules wherein the sense region comprises instant SEQ ID NO: 7.

Ambion teaches a siRNA target finder and design tool and teaches that the algorithms followed the guidelines for siRNA design to generate a report indicating preferential sense and antisense siRNA oligonucleotides for a given mRNA sequence.

It would have been obvious to design a siRNA with the preferable structural characteristics taught by Reich et al. and Fosnaugh et al., as discussed in the rejection

under 35 U.S.C. 103(a) above, wherein the sense region comprises instant SEQ ID NO: 7.

One would have been motivated to specifically design the siRNA targeted to HIF-1α of Reich et al. to comprise instant SEQ ID NO: 7 because Ambion teaches an algorithm, wherein insertion of the published HIF-1α sequence (GenBank accession number NM_001530) results in the identification of hotspots and preferential siRNA sequences and specifically identified instant SEQ ID NO: 7 as a preferred target sequence.

The Ambion results are as follows:

siRNA Converter and RNA Oligo Calculator

Sense siRNA:	GAUGACAUGAAAGCACAGAtt extinction coefficient = 220900 $M^{-1}cm^{-1}$ MW = 6763.2 nmol per OD260 = 4.53 µg per OD260 = 30.62 sense strand length: 21
Antisense siRNA:	UCUGUGCUUUCAUGUCAUCtt extinction coefficient = 193000 $M^{-1}cm^{-1}$ MW = 6522.2 nmol per OD260 = 5.18 µg per OD260 = 33.79 antisense strand length: 21

Alignment

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Target:                          5'- AAGATGACATGAAAGCACAGA -3'

Sense siRNA strand:              5'-   GAUGACAUGAAAGCACAGAtt -3'
Antisense siRNA strand:          3'- ttCUACUGUACUUUCGUGUCU -5'
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Since it was known to target and inhibit HIF-1α with siRNA molecules, as evidenced by Reich et al., one would have been motivated to insert the known HIF-1α sequence (GenBank accession number NM_001530, as disclosed in the instant specification on page 13) into the publicly accessible Ambion algorithm to determine preferred siRNA duplexes specific for HIF-1α.

Finally, one of skill in the art would have had a reasonable expectation of success at generating a siRNA duplex comprising instant SEQ ID NO: 7 because Ambion specifically teaches a method of designing a siRNA with an algorithm and generates the instant sequence and Reich et al. and Fosnaugh et al. teach preferred structural characteristics for siRNA molecules, the siRNA molecules of Reich et al. being specifically targeted to HIF-1α.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMY H. BOWMAN whose telephone number is

(571)272-0755. The examiner can normally be reached on Monday-Thursday 6:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Amy H. Bowman/
Examiner, Art Unit 1635